IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : George L. King
Serial No. : 10/027,204
Filed : December 21, 2001
Title : PKC MONOCYTE ASSAY

Art Unit : 1651
Examiner : Ralph J. Gitomer

Mail Stop Appeal Brief - Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

BRIEF ON APPEAL

(1) Real Party in Interest

The real party in interest is Joslin Diabetes Center, Inc., One Joslin Place, Boston, MA 02215.

(2) Related Appeals and Interferences

There are no pending related appeals or interferences.

(3) Status of Claims

Claims 16-22 are rejected.

Claims 1-15 and 23-43 have been canceled.

A notice of appeal was filed on February 3, 2004.

(4) Status of Amendments

No amendments are being submitted herewith.

CERTIFICATE OF MAILING BY FIRST CLASS MAIL

I hereby certify under 37 CFR §1.8(a) that this correspondence is being deposited with the United States Postal Service as first class mail with sufficient postage on the date indicated below and is addressed to the Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

June 2, 2004
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(5) Summary of Invention

The invention relates to a method of evaluating a human or an animal subject for the extent, stage, or severity of a cardiovascular complication of diabetes. The method includes determining the level of protein kinase C ("PKC") activity in the monocytes of the subject, optionally comparing the determined activity to a standard, and correlating the determined activity with the extent, stage, or severity of a cardiovascular complication of diabetes. One embodiment of the invention includes determining the level of PKC Beta activity. Specific cardiovascular complications evaluated can include: diabetic retinopathy, diabetic nephropathy, hypertension, atherosclerosis, coronary artery spasm, congestive heart failure, coronary artery disease, valvular disease, arrhythmias, and cardiomyopathy.

(6) Issues

Are claims 16-22 obvious over Giulio Ceolotto et al., *Protein Kinase C Activity Is Acutely Regulated by Plasma Glucose Concentration in Human Monocytes In Vivo*, 48 Diabetes 1316 (1999) ("Ceolotto")?

(7) Grouping of Claims

Claims 16-22 stand or fall together.

(8) Argument

Claims 16-22 were rejected under 35 U.S.C § 103(a) as being obvious over Ceolotto. These rejections are respectfully traversed.

Section 103(a) of the Patent Act states that:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

35 U.S.C. § 103(a). Obviousness is a question of law, based on underlying factual inquiries. *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966); *McGinley v. Franklin Sports, Inc.*, 262 F.3d

1339, 1349 (Fed. Cir. 2001). The four factual inquiries have been set out by the Supreme Court and include: (1) the scope and content of the prior art; (2) the differences between the prior art and the claims at issue; (3) the level of ordinary skill in the pertinent art; and (4) secondary considerations, such as commercial success, long-felt but unsolved needs or failure of others. *Graham*, 383 U.S. at 17-18; *McGinley*, 262 F.3d at 1349.

With the *Graham* factors in mind, the examiner must prove three criteria to establish a *prima facie* case of obviousness. First, the reference must teach or suggest all limitations of the claims at issue. M.P.E.P. § 2143. Second, there must be some suggestion or motivation in the prior art or in the knowledge generally available to modify the reference. *Brown & Williamson Tobacco, Corp. v. Philip Morris, Inc.*, 229 F.3d 1120, 1124-25 (Fed. Cir. 2000); *In re O'Farrell*, 853 F.2d 894, 902 (Fed. Cir. 1988); M.P.E.P. § 2143. Third, there must be evidence suggesting that the modification would be successful. *Brown & Williamson Tobacco, Corp.*, 229 F.3d at 1124-25; *In re O'Farrell*, 853 F.2d at 902; M.P.E.P. § 2143.

Ceolotto does not teach all the limitations of the claims at issue, does not provide a motivation to modify the reference and does not suggest that such modification would be successful. The pending claims are narrowly drawn to a method of evaluating a subject for the extent, stage, or severity of a cardiovascular ("CV") complication of diabetes. The method includes determining the level of PKC activity in monocytes of the subject and correlating the level of PKC activity with the extent, stage, or severity of a CV complication of diabetes.

The Examiner asserts that:

> It is the Examiner's position that Ceolotto discusses the relevance of the study to diabetic complications generally and atherosclerosis specifically. Retinopathy and nephropathy are well known complications of diabetes.

Ceolotto, however, does not teach all the limitations of the claims at issue. Ceolotto's statement that monocyte PKC activity "may be relevant to the study of development of diabetic complications," to which the Examiner seems to be referring in the above-quoted passage, does not suggest a diagnostic correlation, much less a highly specific diagnostic correlation related to the extent, stage, or severity of CV diabetic complications (see Ceolotto page 1321, second column, last sentence). The Examiner's argument does not address this explicit limitation of the claims at all and, in fact, seems to ignore this limitation. In particular, the office action does not

point out what in Ceolotto would make a correlation of monocyte PKC activity with extent, stage, or severity of CV diabetic complications obvious.

Additionally, Ceolotto does not provide the required motivation and reasonable expectation of success to correlate monocyte PKC activity with CV diabetes complications, much less with the extent, stage, or severity of such complications as claimed, and even less with the specific CV complications recited in the dependent claims. Indeed, the claims relate to a completely different patient population than that examined in Ceolotto. The type 2 diabetic subjects of the Ceolotto study were **free of peripheral vascular disease, free of atherosclerotic cardiovascular disease and "[p]atients with proliferative retinopathy or significant renal impairment [i.e., nephropathy] were also excluded**" from the subject population (see Ceolotto, paragraph bridging pages 1316-1317 and page 1317, first full paragraph of first column). Thus, Ceolotto purposely excluded the particular patient population (those having CV complication of diabetes) recited in the present claims. A skilled artisan would have absolutely no motivation to make predictions about a particular patient population based on a study where that specific patient population was excluded.

Ceolotto also does not suggest a reasonable expectation of success in making a correlation between monocyte PKC activity and CV complications of diabetes. The Federal Circuit admonished that it is not "obvious to try" to "explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it." *In re O'Farrell*, 853 F.2d at 903.

Indeed, the fact that patients having CV complications of diabetes were excluded in Ceolotto shows that such patients might be expected to affect the results in an unpredictable manner. Additionally, Ceolotto teaches that in some cases monocyte PKC activity is upregulated during hyperglycemia (see Ceolotto Figure 2 page 1318), while in other cases, that is in patients with poorly controlled diabetes "a progressive downregulation of PKC activity, at least in monocytes" may be induced (see Ceolotto page 1320, left column). Therefore Ceolotto only provides general guidance that there is some correlation between monocyte PKC activity and hyperglycemia. It is not even clear whether it is a positive or a negative correlation. And its general guidance excludes the specific patient populations on which the claims at issue focus.

Therefore, Ceolotto does not provide a reasonable expectation of success to arrive at the claimed method.

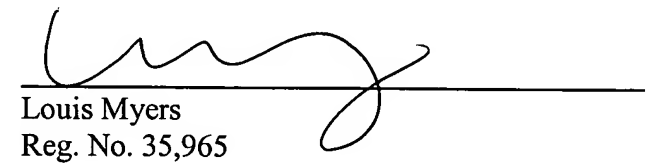
In sum, because patients with CV complications were not even part of Ceolotto's study, Ceolotto does not teach all the limitations of the claims at issue and does not provide the required motivation and reasonable expectation of success to correlate monocyte PKC activity with CV diabetes complications, much less with the more narrow extent, stage, or severity of such complications, as claimed, and even less with the specific CV complications recited in the dependent claims.

In view of the foregoing, Applicants assert that the pending claims are in condition for allowance, of which action is requested.

The brief fee of $165 is enclosed. Also enclosed is a Petition for Extension of Time, along with the required fee. Please apply any other charges or credits to Deposit Account No. 06-1050, referencing attorney docket number 10276-066001.

Respectfully submitted,

Date: 2 Jun 04



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Appendix of Claims

Claim 16. A method of evaluating a subject for the extent, stage, or severity, of a cardiovascular complication of diabetes, the method comprising:

determining the level of PKC activity in monocytes of the subject;

optionally comparing the level of the PKC activity in monocytes of the subject with a standard, and

correlating the level of PKC activity with the extent, stage, or severity, of the cardiovascular complication of diabetes.

Claim 17. The method of claim 16, wherein the diabetic complication is diabetic retinopathy.

Claim 18. The method of claim 16, wherein the diabetic complication is diabetic nephropathy.

Claim 19. The method of claim 16, wherein the diabetic complication is hypertension, atherosclerosis, coronary artery spasm, congestive heart failure, coronary artery disease, valvular disease, arrhythmias, or cardiomyopathy.

Claim 20. The method of claim 16, wherein the PKC activity is PKC β activity.

Claim 21. The method of claim 16, wherein the subject is a human.

Claim 22. The method of claim 16, wherein the subject is an experimental animal.